Exhibit 21

Aurobindo Toxicology Health Hazard Assessment

Valsartan and Valsartan/Amlodipine Tablets, Film Coated

Complaint No. N/A

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Overview

Aurobindo has requested a Toxicology Health Hazard Assessment because an impurity — N-nitrosoethylamine (NDEA) — was determined to be present at >0.0883 ppm (88.3 ng/mL in Valsartan Tablets and Valsartan/Amlodipine Tablets, Film-Coated. This concentration is out of specification and exceeds the maximum acceptable concentration as determined by the FDA. NDEA is classified as a known animal carcinogen and a suspected human carcinogen. Valsartan and other drugs classified as sartans (e.g., irbesartan, losartan) are angiotensin II receptor blockers (ARBs) alone or in combination with other antihypertensive agents are maintenance drugs for hypertension.

Background

In July 2018, N-nitrosomethylamine (NDMA) was found in the active pharmaceutical ingredient (API) used to manufacture valsartan by Zhejiang Huahai Pharmaceutical Company in Linhai, China, and a number of generic products using this API subsequently were recalled by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). According to records from Zhejiang Huahai, the FDA indicated that some levels of this carcinogenic impurity may have been in the valsartan-containing products for as long as 4 years. On July 13, 2018 the FDA issued a recall of particular batches of NDMA-containing valsartan tablets.

Subsequently, on or about September 15, 2018, NDEA was found in one batch of losartan manufactured in India by Hetero Labs, and Zhejiang Huahai also detected NDEA in some lots of its valsartan API. Testing by the FDA confirmed the presence of NDEA in several lots of valsartan API and in three lots of valsartan distributed by Torrent Pharmaceuticals, which used the Zhejiang Huahai API. As a precaution and to ensure that manufacturing process changes or other factors have not resulted in systemic contamination of sartan drugs already on the market, the EMA on September 21, 2018 expanded its review of nitrosamine impurities to include irbesartan, candesartan, losartan and olmesartan in addition to valsartan. Like valsartan, these active substances have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of impurities such as NDEA.

On September 28, 2018 the FDA placed Zhejiang Huahai on import alert, banning all API made by Zhejiang Huahai and all finished drug products produced with Zhejiang Huahai's API from legally entering the United States, "to protect U.S. patients while the API manufacturer fully determines how impurities were introduced into its API and remediates its quality systems." During October and November 2018, the FDA developed and validated an accurate method for measuring the concentration of NDEA in sartans and identified out of specification concentrations of NDEA in a number of generic lots marketed by Sandoz, Mylan, and Teva, which were recalled voluntarily. On December 19, 2018 the FDA published interim acceptable intake levels for NDEA and NDMA in the ARB class [Table 1 in Appendix].

On December 20, 2018, the FDA reported a voluntary recall of losartan tablets by Torrent Pharmaceuticals because of out of specification concentrations of NDEA.

Valsartan Recall by Aurobindo

On December 31, 2018, Aurobindo voluntarily recalled 80 lots of Valsartan/Hydrochlorothiazide, Valsartan/Amlodipine and Valsartan 320 mg tablets due to trace amounts NDEA found in the finished drug product. These voluntarily recalled lots are listed in the Table 2 in the Appendix.

Toxicology of NDEA

The health risk of most concern for nitrosamines generally is carcinogenicity. Exposure to nitrosamines has been shown to produce tumors in laboratory animals and has been linked in epidemiologic studies to human cancer including pancreatic cancer and brain tumors in children. Nitrosamines generally are classified by a number of international organizations and regulatory authorities based on potential carcinogenicity. In contrast to NDMA, which has been determined to increase the risk of cancer in humans over a prolonged period of exposure, the potential human carcinogenicity to NDEA is not as well documented. Under the International Agency for Research on Cancer (IARC), which is part of the World Health Organization, NDEA is classified as a group 2A substance (probably carcinogenic in humans). The EU classifies NDEA as Category 1B (presumed to have carcinogenic potential in humans, based largely on animal evidence). In the U.S., the EPA classifies NDEA as Category B2 (probable human carcinogen) under its 1986 carcinogen assessment guidelines, which means that animal data providing a causal relationship of carcinogenicity are available, but human data are limited.

It has been demonstrated that liver cancer can be induced in rats by the oral administration of NDEA at a concentration of 0.02% over time. Nitroso compounds such as NDEA are known to cause hepatoportal sclerosis, hepatolobular dilation, hepatic fibrosis and necrosis, liver enlargement, pre-neoplastic lesions, and cirrhosis in rats. NDEA is degraded by the action of the cytochrome P450-dependent monooxygenase system to form its active ethyl radicals (CH_3CH^{2+}). These ethyl radicals and other reactive products interact with DNA, leading to mutations and elevations in blood serum enzyme markers such as aspartate-transaminase (AST), alanine-aminotransferase (ALT), alkaline-phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate-dehydrogenase (LDH), and total bilirubin. Ethyl radicals formed by the degradation of NDEA also produce an increase in oxidative stress markers such as lipid peroxidation, protein carbonyl content, superoxide dismutase, and catalase, and can cause neoplastic transformation in liver tissues.

There is also some experimental evidence that NDEA may contribute to the atherosclerotic process, at least in rabbits. Oral administration of NDEA at a dose of 50 mg/day together with a hypercholesterolemic diet to rabbits resulted in a significant increase in osmotic fragility of erythrocytes as well as increased *in vitro* lipid peroxidation (LPO) of erythrocytes. The plasma total lipids, cholesterol and glycerides continued to increase during the feeding of the hypercholesterolemic diet with or without NDEA. However, after the cessation of the hypercholesterolemic diet, the decrease in the lipid fractions was relatively less in the experimental group receiving NDEA. Administration of NDEA in the hypercholesterolemic diet did not affect the total lipid content in the liver, although it marginally increased the hepatic cholesterol levels. Histopathologic changes in different tissues (heart, aorta and liver) were relatively more severe in experimental rabbits receiving NDEA compared with controls. This study suggests that oral administration of NDEA results in increased LPO of blood and decreased lipid clearance, which may in turn result in an increased degree of atherosclerosis.

Exogenous sources (mainly, drinking water and food) account for most of the exposure to N-nitrosamines such as NDEA. Different risk assessments have calculated drinking water concentrations of nitrosamines generally that are associated with carcinogenic risk to range from 0.7-100 ng/L. A literature search revealed only one publication, which addressed hepatocellular carcinoma induction by NDEA in a rat model of primary liver cancer. Besides being present in food items like cheese, smoked, salted, and dried fish, cured meat, and alcoholic beverages, it is also found in the effluents and smoke released from rubber, dye, metal industries, and cigarettes. Specific NDEA content of certain foods includes:

- Pork liver: Not detected
- Pork belly: Not detected
- Pork meat in salt: 0.06-0.07 µg/kg
- Smoked pork brisket: 0.06-9.5 µg/kg

Material Safety Data list the acute oral LD_{50} of NDEA to be 220 mg/kg in rats, 200 mg/kg in mice, and 250 mg/kg in Guinea pigs.

Summary

The potential/probable human carcinogen NDEA has been determined to be present at >0.0883 ppm in Aurobindo's Valsartan Tablets, Valsartan/Hydrochlorothiazide Tablets, and Valsartan/Amlodipine Tablets, Film-Coated. These concentrations are out of specification and exceed the FDA's maximum acceptable concentration. However, in contrast to NDMA, which has been determined to increase the risk of cancer in humans over a prolonged period of exposure, the potential human carcinogenicity to NDEA is not as well documented. Based on a relative risk assessment by the FDA, short-term exposure to what appear to be low levels of NDEA should not result in any significantly increased risk of carcinogenesis. In addition, the EMA has determined that, based on the trace amounts of NDEA seen so

far in one batch of losartan from Hetero Labs, there is no immediate risk to patients. Patients are therefore advised not to stop taking losartan or other sartan medicines without speaking to their doctor. Nevertheless, since the FDA has recalled some valsartan-containing products because of the presence of NDEA impurities, it cannot be stated with absolute certainty that there is no long-term risk.

Conclusion

Short-term exposure to what appear to be relatively low levels of NDEA in Aurobindo's Valsartan Tablets, Valsartan/Hydrochlorothiazide Tablets, and Valsartan/Amlodipine Tablets, Film-Coated should not result in any acute toxicity or significantly increased risk of carcinogenesis. However, since the FDA has recalled some valsartan-containing products because of NDEA impurities, it cannot be stated with absolute certainty that there is no long-term risk of carcinogenesis. Accordingly, lots of Aurobindo's Valsartan Tablets, Valsartan/Hydrochlorothiazide Tablets, and Valsartan/Amlodipine Tablets, Film-Coated have been recalled voluntarily.

References

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APPENDIX

Table 1.

Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**
Valsartan	320	96	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088
Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer
risk after 70 years exposure
** These values are based on a drug's maximum daily dose as reflected in the drug label

Table 2

Table 2. Analytical Results for the Batches Having NDEA Content Exceeding the Specified Limit

S. No.	ANDA	Generic Name of Drug Product	Dosage Strength	Package Size	NDC Number	Lot Number(s) and Expiration Date(s)	NDMA	NDEA (ppm)
43	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17056-A; 10/2020	Not Detected	0.121
44	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17057-A; 10/2020	Not Detected	0.095
45	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17058-A; 10/2020	Not Detected	0.101
46	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17059-A; 10/2020	Not Detected	0.119
47	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17060-A; 10/2020	Not Detected	0.103
48	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17062-A; 10/2020	Not Detected	0.083
49	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17066-A; 10/2020	Not Detected	0.121
50	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17067-A; 11/2020	Not Detected	0.191

51	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HOPE Container	65862-551-90	HTSB17068-A; 11/2020	Not Detected	0.098
52	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17069-A; 11/2020	Not Detected	0.167
53	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB18001-A; 12/2020	Not Detected	0.196
54	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB18002-A; 12/2020	Not Detected	0.201
55	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	901s HDPE Container	65862-551-90	HTSB18003-A; 12/2020	Not Detected	0.141
56	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB18004-A; 12/2020	Not Detected	0.206
57	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB18005-A; 12/2020	Not Detected	0.135
58	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB18006-A; 12/2020	Not Detected	0.146
59	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB18007-A; 12/2020	Not Detected	0.113

60	202519	Valsartan and Hydrochlorothiazide tablets USP	80mg/12.5mg	90's HDPE Container	65862-547-90	HVSA17011-A; 11/2020	Not Detected	0.109
61	202519	Valsartan and Hydrochlorothiazide tablets USP	80mg/12.5mg	90's HDPE Container	65862-547-90	HVSA17012-A; 11/2020	Not Detected	0.107
62	202519	Valsartan and Hydrochlorothiazide tablets USP	80mg/12.5mg	90's HDPE Container	65862-547-90	HVSA18001-A; 12/2020	Not Detected	0.090
63	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB17023-A; 08/2020	Not Detected	0.087
64	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB17036-A; 11/2020	Not Detected	0.143
65	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB17037-A; 11/2020	Not Detected	0.162
66	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25 mg	90's HDPE Container	65862-549-90	HVSB17038-A; 11/2020	Not Detected	0.125
67	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB17039-A; 11/2020	Not Detected	0.173
68	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB17040-B; 11/2020	Not Detected	0.119

69	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Contain	65862-549-90	HVSB18001-A; 12/2020	Not Detected	0.150
70	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB18002-A; 12/2020	Not Detected	0.154
71	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB18003-A; 12/2020	Not Detected	0.142
72	202519	Valsartan and Hydrochlorothiazide tablets USP	160mg/25mg	90's HDPE Container	65862-549-90	HVSB18004-A; 12/2020	Not Detected	0.138
73	202519	Valsartan and Hydrochlorothiazide Tablets USP	160mg/12.5mg	90's HDPE Container	65862-548-90	HTSA17037-A; 10/2020	Not Detected	0.097
74	202519	Valsartan and Hydrochlorothiazide Tablets USP	160mg/12.5mg	90's HDPE Container	65862-548-90	HTSA17039-A; 10/2020	Not Detected	0.095
75	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17063-A; 10/2020	Not Detected	0.155
76	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's I-IDPE Container	65862-551-90	HTSB17064-A; 10/2020	Not Detected	0.154
77	202519	Valsartan and Hydrochlorothiazide Tablets USP	320mg/25mg	90's HDPE Container	65862-551-90	HTSB17065-A; 10/2020	Not Detected	0.138

78	202519	Valsartan and Hydrochlorothiazide Tablets USP	320/25mg	90's HDPE Container	65862-551-90	HTSB18029A;03/2021	Not Detected	Not detected*

Valsartan Tablets USP

S. No.	ANDA	Generic Name of Drug Product	Dosage Strength	Package Size	NDC Number	Lot Number(s) and Expiration Date(s)	NDMA	NDEA (ppm)
79	202223	Valsartan Tablets USP	320mg	90	65862-573-90	VUSD17008-A; 07/2019	Not Detected	Not detected*
80	202223	Valsartan Tablets USP	320mg	90	65862-573-90	VUSD17009-A; 09/2019	Not Detected	0.052*

*These batches have been tested by US FDA and found NDEA impurity more than specified limit hence considered for recall.